Novel Antiplatelet Agents

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Director of Cardiovascular Research
Assistant Professor of Medicine
How did we get here?...


Modified from Michel Bertrand
Ticlopidine during PCI with use of Coronary Stents

- Bertrand et al, *Circulation* 1998
The Thienopyridine Family

Ticlopidine

(1st generation)

- P2Y₁₂ ADP receptor antagonism: antithrombotic treatment of choice for coronary stenting
- Side effects: neutropenia, thrombocytopenia, rash, diarrhea, etc
- Delayed time frame to achieve full antiplatelet effects

Solution to these problems:

Clopidogrel

(2nd generation)

- Better Safety profile - Fewer side effects
- Rapid onset of action with a loading dose
- Better clinical outcomes
  (Bhatt DL et al. J Am Coll Cardiol 2002; 39: 9–14.).
The Thienopyridine Family

1) Irreversible platelet inhibitor
2) Interindividual response variability

- Better Safety profile - Fewer side effects
- Rapid onset of action with a loading dose of 300 mg
- Better clinical outcomes

Clopidogrel
(2nd generation)

1) Irreversible platelet inhibitor
2) Interindividual response variability

- bleeding risk in CABG
- full antiplatelet effects not always so rapid
- level of inhibition not always so high
- clopidogrel resistance
Individual Response Variability to Dual Antiplatelet Therapy in the *Steady State Phase* of Treatment

Adapted from Angiolillo DJ et al. *Am J Cardiol.* 2006;97:38-43.
## Clinical Relevance of Clopidogrel Non-responsiveness

### Post-Stent Ischemic Events and Periprocedural Infarction

<table>
<thead>
<tr>
<th>N</th>
<th>Functional Parameter</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matezky et al. Circulation 2004</td>
<td>60 ↑ platelet aggregation (4th quartile)</td>
<td>Post-primary PCI ischemic events (6 months)</td>
</tr>
<tr>
<td>Gurbel et al. JACC 2005</td>
<td>192 ↑ periprocedural platelet aggregation</td>
<td>Post-PCI ischemic events (6 months)</td>
</tr>
<tr>
<td>Gurbel et al. Circulation 2005</td>
<td>120 ↑ periprocedural platelet aggregation</td>
<td>Myonecrosis and inflammation marker release</td>
</tr>
<tr>
<td>Cuisset et al. J Thromb Haemost 2006</td>
<td>106 ↑ platelet aggregation</td>
<td>Post-PCI ischemic events (30 days)</td>
</tr>
<tr>
<td>Lev et al. JACC 2006</td>
<td>120 ↑ clopidogrel/aspirin-resistant patients</td>
<td>Post PCI-myonecrosis</td>
</tr>
<tr>
<td>Cuisset et al. JACC 2006</td>
<td>292 ↑ platelet aggregation</td>
<td>Post-PCI ischemic events (30 days)</td>
</tr>
<tr>
<td>Hochozler et al. JACC 2006</td>
<td>802 ↑ platelet aggregation (3rd &amp; 4th quartiles)</td>
<td>Post-PCI ischemic events (30 days)</td>
</tr>
<tr>
<td>Geisler et al. Eur Heart J 2006</td>
<td>379 ↓ platelet inhibition</td>
<td>Post-PCI ischemic events (3 months)</td>
</tr>
<tr>
<td>Bliden et al. JACC 2007</td>
<td>100 ↑ platelet aggregation</td>
<td>Post-PCI ischemic events (12 months)</td>
</tr>
<tr>
<td>Angiolillo et al. JACC 2007</td>
<td>173 ↑ platelet aggregation (4th quartile)</td>
<td>Ischemic events (24 months)</td>
</tr>
</tbody>
</table>

adapted from Angiolillo DJ et al. Am J Cardiov Drugs. 2007.
### Clinical Relevance of Clopidogrel Non-responsiveness

#### Stent Thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Functional Parameter</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mueller et al. Thromb Haemost 2003</td>
<td>105</td>
<td>↓ inhibition of platelet aggregation</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>Barragan et al. CCI 2003</td>
<td>36</td>
<td>↑ P2Y₁₂ reactivity ratio (VASP-levels)</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>Gurbel et al. JACC 2005</td>
<td>120</td>
<td>↑ P2Y₁₂ reactivity ratio; ↑ platelet aggregation; ↑ stimulated GPIIb/IIIa expression</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>Ajzenberg et al. JACC 2005</td>
<td>49</td>
<td>↑ shear-induced platelet aggregation</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>Buonamici et al JACC 2007</td>
<td>804</td>
<td>↑ platelet aggregation</td>
<td>Stent thrombosis</td>
</tr>
</tbody>
</table>

*adapted from Angiolillo DJ et al. Am J Cardiov Drugs. 2007.*
Ideal ADP P2Y$_{12}$ receptor antagonist

- Rapid onset
- High level of inhibition
- No resistance
- Reversible
Novel ADP P2Y$_{12}$ receptor antagonist

Prasugrel

AZD6140

Cangrelor
Novel ADP P2Y$_{12}$ receptor antagonist

- Prasugrel
- AZD6140
- Cangrelor
The Thienopyridine Family

Ticlopidine
(1\textsuperscript{st} generation)

Clopidogrel
(2\textsuperscript{nd} generation)

Prasugrel (CS-747) (LY640315)
(3\textsuperscript{rd} generation)
Active Metabolite Formation

**Active Metabolite**

**Pro-drug**

**Pre-hepatic metabolism**
*Esterases in blood (Small Intestine)*

**Hepatic Metabolism**
*Cytochrome P450*

---

**Clopidogrel**

85% Inactive Metabolites
*Esterases in blood*

**Active Metabolite**

**Prasugrel**

**Active Metabolite**
Healthy volunteer crossover study
IPA (20 μM ADP) at 24 hours

Brandt J et al. AHJ 2006

Response to clopidogrel
300 mg

Response to prasugrel
60 mg

Inhibition of platelet aggregation (%)

N=64
**Prasugrel vs. Clopidogrel: Stable CAD**

Inhibition of Platelet Aggregation (28 days; 20 \( \mu \text{M ADP} \))

- **Clopidogrel 300/75**
- **Prasugrel 60/15**
- **Prasugrel 60/10**
- **Prasugrel 40/7.5**
- **Prasugrel 40/5**
- **Clopidogrel 300/75**

IPA (%; mean adjusted)

25% IPA

**Jernberg T et al. Eur Heart J 2006; 27: 1166-73.**
STUDY DESIGN

PCI with stenting (N=900)

Study Drug in lab; Stratify for GP IIb/IIIa

PRASUGREL
LD 40 mg
MD 7.5 mg
N=200

PRASUGREL
LD 60 mg
MD 10 mg
N=200

PRASUGREL
LD 60 mg
MD 15 mg
N=250

CLOPIDOGREL
LD 300 mg
MD 75 mg
N=250

Maintenance Rx for 30 days

1° endpoint: Significant (non-CABG) bleeding through 30 D

2° endpoints: MACE through 30 D, Major Bleeding, Component Clinical Endpoints

1° EP: Significant Non-CABG Bleeding 30 D

**Clop. vs Prasugrel**
- P = 0.59

**Dose Ranging**
- P = NS

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Prasugrel LD/MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clop R/N</td>
<td>3/254</td>
</tr>
<tr>
<td>Pras R/N</td>
<td>11/650</td>
</tr>
<tr>
<td>40/7.5</td>
<td>1.5%</td>
</tr>
<tr>
<td>60/10</td>
<td>2.0%</td>
</tr>
<tr>
<td>60/15</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

MACE: Time to Event
Death, MI, CTVT, Stroke, and Recurrent Ischemia

Kaplan-Meier Estimate

- **CLOPIDOGREL**: 9.4%
- **PRASUGREL**: 7.2%

RR = 0.77 [0.5, 1.2]

*p* = 0.26

Time since PCI (days)

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

Double-blind

N= 13,600

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

1° endpoint: CV death, MI, Stroke
2° endpoints: CV death, MI, Stroke, Rehosp-Rec Isch
CV death, MI, UTVR

Stent Thrombosis (ARC definite/prob.)

Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

Median duration of therapy - 12 months
Primary Endpoint CV Death, MI, Stroke

- **Clopidogrel**
  - HR 0.80
  - P = 0.0003
  - 12.1 (781)

- **Prasugrel**
  - HR 0.77
  - P = 0.0001
  - 9.9 (643)

- **HR 0.81**
  - (0.73-0.90)
  - P = 0.0004
  - NNT = 46

- ITT = 13,608
- LTFU = 14 (0.1%)

Wiviott SD et al. NEJM 2007
Timing of Benefit (Landmark Analysis)

Wiviott SD et al. NEJM 2007
Stent Thrombosis (ARC Definite + Probable)

Any Stent at Index PCI
N= 12,844

- Clopidogrel
  - 2.4 (142)
  - HR 0.48
  - P <0.0001
  - NNT= 77

- Prasugrel
  - 1.1 (68)
  - NNT= 77

Wiviott SD et al. NEJM 2007
Balance of Efficacy and Safety

- **CV Death / MI / Stroke**
  - **Prasugrel**: HR 0.81 (0.73-0.90), P=0.0004
  - **Clopidogrel**: HR 1.32 (1.03-1.68), P=0.03
  - **NNT = 46**

- **TIMI Major NonCABG Bleeds**
  - **Prasugrel**: ↓ 35 events
  - **Clopidogrel**: ↑ 138 events
  - **NNH = 167**

Wiviott SD et al. NEJM 2007
Bleeding Events
Safety Cohort
(N=13,457)

TIMI Major Bleeds

- Clopidogrel: ARD 0.6%
  - HR 1.32
  - P=0.03
  - NNH=167

- Prasugrel: ARD 0.5%
  - HR 1.52
  - P=0.01

Life Threatening

- Clopidogrel: ARD 0.2%
  - P=0.03

- Prasugrel: ARD 2.4%

Nonfatal

- Clopidogrel: ARD 0.1%
  - P=0.23

- Prasugrel: ARD 0.9%
  - P=0.002

Fatal

- Clopidogrel: ARD 0%
  - P=0.74

- Prasugrel: ARD 0%

ICH

- Clopidogrel: ARD 0%
  - P=0.74

- Prasugrel: ARD 0%

Wiviott SD et al. NEJM 2007
Net Clinical Benefit
Death, MI, Stroke, Major Bleed (non CABG)

![Graph showing comparison between Clopidogrel and Prasugrel](graph.png)

**Clopidogrel**
- ITT = 13,608
- HR 0.87
- P = 0.004

**Prasugrel**
- HR 13.9
- 12.2
- P = 0.64

**Events per 1000 pts**
- MI: Clop -3.2%, Pras -3.0%
- Major Bleed (non CABG): P = 0.64

**All Cause Mortality**
- Clop 3.2%
- Pras 3.0%

**Inset**
- MI: Clop -23, Pras +6
- Major Bleed (non CABG): Clop -23, Pras +2

Wiviott SD et al. NEJM 2007
CV Death, MI, Stroke
Major Subgroups

Reduction in risk (%)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Prasugrel Better</th>
<th>Clopidogrel Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA/NSTEMI</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>STEMI</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>&lt;65</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>65-74</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>≥75</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>No DM</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>DM</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>BMS</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>DES</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>GPI</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>No GPI</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>CrCl &lt; 60</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>CrCl ≥ 60</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>OVERALL</td>
<td>19</td>
<td>P_{inter} = NS</td>
</tr>
</tbody>
</table>
Diabetic Subgroup

N=3146

CV Death / MI / Stroke

TIMI Major NonCABG Bleeds

Clopidogrel

Prasugrel

Endpoint (%)

Days

HR 0.70
P<0.001
NNT = 21

Wiviott SD et al. NEJM 2007
Net Clinical Benefit

Bleeding Risk Subgroups

Post-hoc analysis

Prior Stroke / TIA

Yes

No

Risk (%)

+54

P_{int} = 0.006

-16

Age

>=75

<75

Wgt

<60 kg

>=60 kg

Risk (%)

-1

P_{int} = 0.18

-16

+3

P_{int} = 0.36

-14

OVERALL

-13

Wiviott SD et al. NEJM 2007
Bleeding Risk Subgroups

Therapeutic Considerations

- Significant Net Clinical Benefit with Prasugrel 80%
- Reduced MD
  - Guided by PK
  - Age ≥ 75 or Wt < 60 kg
- Avoid Prasugrel
- Prior CVA/TIA

MD 10 mg

Wiviott SD et al. NEJM 2007
### Conclusions

Higher IPA to Support PCI

**Prasugrel 60 mg LD/10mg MD vs Clopidogrel 300 mg LD/75 mg MD**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A significant reduction in:</td>
<td>Significant increase in serious bleeding</td>
</tr>
<tr>
<td>CV Death/MI/Stroke</td>
<td>(32% increase)</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>Avoid in pts with prior CVA/TIA</td>
</tr>
<tr>
<td>uTVR</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td></td>
</tr>
<tr>
<td>2. An early and sustained benefit</td>
<td></td>
</tr>
<tr>
<td>3. Across ACS spectrum</td>
<td></td>
</tr>
</tbody>
</table>

Net clinical benefit significantly favored Prasugrel

Optimization of Prasugrel maintenance dosing in a minority of patients may help improve the benefit: risk balance

Wiviott SD et al. NEJM 2007
Comparison with Higher Dose Clopidogrel

IPA (%; 20 µM ADP)

N=201  P<0.0001 for each

Prasugrel 60 mg

Clopidogrel 600 mg

Prasugrel studies in the pipeline

- **S.W.A.P.** – Phase II: Switching antiplatelet therapy (clopidogrel to prasugrel)
- **ACAPULCO** – Phase II: Prasugrel vs high dose clopidogrel in ACS/PCI
- **TRILOGY** – Phase III: Prasugrel vs clopidogrel in non-revascularized ACS
Novel ADP P2Y$_{12}$ receptor antagonist

Prasugrel

AZD6140

Cangrelor
AZD6140

- A non-thienopyridine, in the chemical class CPTP (CycloPentylTriazoloPyrimidine)

- First oral reversible ADP P2Y\textsubscript{12} receptor antagonist

- Direct acting via the P2Y\textsubscript{12} receptor - metabolism not required for activity

- More potent platelet inhibitor than clopidogrel
DISPERSE: Faster, Greater and More Consistent IPA with AZD6140 vs clopidogrel

AZD6140 (100 mg bd) vs Clopidogrel

Husted SE et al Eur Heart J 2006; 27: 1038-1047
DISPERSE2 Study Design

- DISPERSE2 was a double-blind, randomized study of AZD6140 compared with clopidogrel, both on a background of aspirin (75–100 mg od)
- 50% of patients in each AZD6140 arm received a loading dose of 270 mg
- In the clopidogrel arm, thienopyridine treatment-naïve patients received a 300-mg loading dose

DISPERSE-2: Final Inhibition of Platelet Aggregation (IPA) (Clopidogrel-Naïve Patients)

**Day 1**

- AZD6140 90 mg
- AZD6140 180 mg
- AZD6140 270 mg
- Clopidogrel 300 mg

**Day 28**

- AZD6140 90 mg
- AZD6140 180 mg
- AZD6140 270 mg
- Clopidogrel 300 mg

*P*<0.05 for both AZD6140 groups vs clopidogrel at 4 h on day 1 and for 180 mg on day 28 and for 90 mg at 0 and 12 h on day 28

**DISPERSE2** Adjudicated Bleeding Rates (%)  
Week 4 and Overall

- **Week 4**
  - **Minor bleeding**
    - AZD6140 90 mg bid N = 334: 9.6%
    - AZD6140 180 mg bid N = 323: 7.7%
    - Clopidogrel 75 mg qd N = 327: 8.0%

- **Major bleeding**
  - AZD6140 90 mg bid N = 334: 6.3%
  - AZD6140 180 mg bid N = 323: 5.3%
  - Clopidogrel 75 mg qd N = 327: 4.7%

- **Overall**
  - **Minor bleeding**
    - AZD6140 90 mg bid N = 334: 6.8%
    - AZD6140 180 mg bid N = 323: 5.8%
    - Clopidogrel 75 mg qd N = 327: 4.4%

  - **Major bleeding**
    - AZD6140 90 mg bid N = 334: 9.9%
    - AZD6140 180 mg bid N = 323: 9.0%
    - Clopidogrel 75 mg qd N = 327: 5.6%

- Adjudicated total bleeding rates were similar for all groups.
- No evidence of dose-response for major bleeds.

*Minor bleeding without major bleeding*

DISPERSE2
Cumulative adjudicated clinical end point of CV death/MI/stroke

- No significant differences found between the groups for clinical end points

## DISPERSE2

**Non-bleeding adverse events (%)**

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>AZD6140 90 mg bid n=334</th>
<th>AZD6140 180 mg bid n=323</th>
<th>Clopidogrel 75 mg qd n=327</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>10.5</td>
<td>15.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7.5</td>
<td>7.4</td>
<td>8.9</td>
</tr>
<tr>
<td>Headache</td>
<td>9.6</td>
<td>6.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.6</td>
<td>6.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4.8</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.4</td>
<td>4.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.0</td>
<td>7.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.2</td>
<td>3.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- Discontinuation rates due to adverse events were low and similar between the groups
  - 21 (6%), 23 (7%) and 19 (6%) discontinued in the AZD6140 90 mg bid, AZD6140 180 mg bid and clopidogrel 75 mg qd groups, respectively
Ventricular Pauses >2.5 Seconds in Context of Other Studies

- Study A: 3.2%
- Study B: 4.8%
- Clop: 4.4%
- AZD6140 90 mg: 5.6%
- AZD6140 180 mg: 9.9%

Clopidogrel-treated patients in 2 different early ACS trials

Patients from DISPERSE2
Primary endpoint: CVD/MI/stroke
Secondary endpoint: CVD/MI/stroke/revascularization with PCI; CVD/MI/stroke, severe recurrent ischemia

ASA = acetylsalicylic acid; bid = twice daily; CVD = cardiovascular disease; ld = loading dose; MI = myocardial infarction; NSTEMI = non-ST-segment elevation MI; qd = once daily; STEMI = ST-segment elevation MI; UA = unstable angina.

ClinicalTrials.gov Identifier: NCT00391872
Novel ADP P2Y$_{12}$ receptor antagonist

- Prasugrel
- AZD6140
- Cangrelor
Cangrelor (AR-C69931MX)

- **Parenteral** ADP-P2Y\textsubscript{12} receptor antagonist

- **ATP analogue**

- **Direct and Reversible** P2Y\textsubscript{12} inhibitor

- **More potent** than clopidogrel ~90% inhibition of platelet aggregation at 1 - 4 mcg/kg/min iv

- **Plasma half-life** of 5-9 min.; 20 min. for return to normal platelet function
Key Phase I result

Rapid reversal of dose-dependent effect

% Inhibition of Aggregation

+ placebo

+ aspirin/heparin/GTN

AR-C69931 (ng.kg\(^{-1}.min\(^{-1}\)) Stepped infusion period

Recovery period
Cangrelor with Clopidogrel

Cangrelor improves platelet inhibition in patients receiving chronic clopidogrel

% inhibition of aggregation response induced by ADP 10µM

Cangrelor + tPA in STEMI

ST Recovery

- TPA
- 931 lo
- 931 med
- 931 hi

Greenbaum et al. ACC 2002.
Phase II clinical data: Compared with Abciximab in PCI

Double-blind randomized trial performed in US

Incidence of events up to 7-days

Death, MI, revascularization

- Abciximab (N=94): 5.4%
- Cangrelor (N=105): 5.7%

Major bleed (TIMI criteria)

- Abciximab (N=94): 2.1%
- Cangrelor (N=105): 1.0%

AR-C69931MX report number SC931-5129 Part 2

Greenbaum et al. Am Heart J. 2006;151:689.e1-689.e10
CHAMPION-PCI

1:1 Double blind, double dummy

Placebo capsules (to match) + Cangrelor bolus (30µg/kg) & infusion (4µg/kg/hour) + Placebo bolus & infusion (to match)

PCI (with or without stent)

Index Procedure
Study drug infusion (for at least 2 hours or the duration of the procedure, whichever is longer)

Clopidogrel capsules (600mg) + Placebo capsules (to match)

Clopidogrel Maintenance (at physician discretion)

1º Endpoint: Death, MI, and uRevasc at 48 hours

2º Endpoints:
Death, MI, uRevasc at 30 days
Death at 6 months and 1 year
Subjects who require PCI
(with or without stent) excluding STEMI

1:1 randomization to two treatment groups
Double blind, placebo-controlled
All patients treated with usual care

Study drugs

Cangrelor
bolus (30 µg/kg) & infusion (4 µg/kg/min)

Placebo
bolus & infusion (to match)

Index procedure

Subjects who require PCI
Study drug infusion: for at least 2 hours or the duration of the procedure, whichever is longer

Immediately post procedure

Placebo capsules
to match

Clopidogrel capsules
(600 mg)

Immediately post-infusion

Clopidogrel capsules
(600 mg)

Placebo capsules
to match

Post-infusion treatment
Aspirin and clopidogrel maintenance dose per local practice

Endpoints

48 hours after randomization
• Primary efficacy endpoint: composite incidence of all-cause mortality, MI, and IDR
• Secondary efficacy: incidence of individual components, stroke & abrupt vessel closure
• Safety endpoints: hemorrhage and transfusion
• Safety: AEs/SAEs

Follow up
• All-cause mortality, MI, IDR at 30 days
• Secondary efficacy: incidence of components at 30 days
• All-cause mortality at 6 months (ascertained at 1 year) and 1 year
Will New P2Y_{12} Inhibitors Reduce Resistance?

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Cangrelor</th>
<th>AZD6140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>High level of inhibition</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Reversible</td>
<td>✗</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>No resistance</td>
<td>😊</td>
<td>😊</td>
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</tbody>
</table>

More potent and less variability!!
Better Clinical Outcomes?!!
Platelet Stimuli

- GP IIb/IIIa integrin
- ADP
- Epinephrine
- Collagen
- Serotonin
- Shear rate
- Thrombin
- Thrombin
- Thrombin

Platelet Aggregation

- AA
- COX-1
- TxA$_2$
- TxA$_2$
- TxA$_2$

GP IIb/IIIa integrin
Thrombus Formation

Two key elements: **cellular** (platelets) and **plasmatic** (coagulation factors)
Platelet Receptors

- Thrombin
- ADP
- Thromboxane A2
- Collagen
- GP Ibα-IX-V
- P2Y-1
- P2Y-12
- PAR-1
- PAR-4

Platelet surface interactions:

- Anionic phospholipid surfaces
- GPIbα-IX-V
- GP IIb IIIa
- Fibrinogen

Platelet receptors:

- GPIa
- GP IIb
- GP IIIa
Activation of PAR1 by thrombin

Thrombin

PAR1

extracellular
plasma membrane

intracellular

LDPR
SFLRNP

PAR1

recognition

cleavage

LDPR
NRLLFS

+ G protein activation

S. R. Coughlin et al. Cell. 1991, 64, 1057
Oral Anti-PAR-1 receptors

Non-Urgent PCI or Cath possible PCI (All Receive Aspirin)
Randomization #1 — 3:1 SCH530348:Placebo (Single Loading Dose)
Sequential Groups: 1=10 mg; 2=20 mg; 3=40 mg, or Placebo

Cardiac Catheterization
Planned PCI (All Receive Clopidogrel and Antithrombin)

Randomization #2 1:1:1
Maintenance Therapy Once Daily for ~ 60 days
SCH 530348 Loading Dose → SCH 530348
Or Placebo Loading Dose → Placebo
SCH 530348

Safety: TIMI Major plus Minor Bleeding
Efficacy: Death/MACE

* Primary Evaluable Cohort

No PCI**
CABG
Medical Management
Quantify Postoperative Chest-Tube Drainage, Transfusions, and Re-exploration
Safety: TIMI Major plus Minor Bleeding

**Secondary Evaluable Cohort
PCI Cohort

TIMI Major/Minor Bleeding

- Placebo: 3.3% (n=151)
- All TRA: 2.8% (n=422)
- 10 mg: 1.6% (n=129)
- 20 mg: 2.5% (n=120)
- 40 mg: 4.0% (n=173)

p-value relative to placebo

p = 0.77
p = 0.35
p = 0.70
p = 0.73

SCH 530348
60-Day Death or MACE

Placebo: 8.6% (n=151)
All TRA: 5.9% (p = 0.26, n=422)
10 mg: 5.0% (p = 0.25, n=129)
20 mg: 4.6% (p = 0.15, n=120)
40 mg: 4.6% (n=173)

p-value relative to placebo

SCH 530348
PCI Cohort

Myocardial Infarction

- Placebo
- 10mg
- 20mg
- 40mg

$p = 0.52$
$p = 0.28$
$p = 0.12$

Days

0 1 2 3 4 5 6 7
Platelet Aggregation Substudy

Subjects with >80% IPA to 15 \( \mu \text{M} \) TRAP

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo n=23</th>
<th>10 mg n=15</th>
<th>20 mg n=18</th>
<th>40 mg n=33</th>
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<tbody>
<tr>
<td>30 minutes</td>
<td>0</td>
<td>6</td>
<td>53</td>
<td>68</td>
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<tr>
<td>60 minutes</td>
<td>0</td>
<td>46</td>
<td>53</td>
<td>82</td>
</tr>
<tr>
<td>90 minutes</td>
<td>21</td>
<td>43</td>
<td>6</td>
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<tr>
<td>120 minutes</td>
<td>43</td>
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<td>96</td>
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</table>

SCH 530348

T·R·A·PCI
TRA (SCH 530348) Program

Evaluation of Efficacy and Safety in Acute and Chronic Atherothrombosis

NSTEACS
10,000 pts

2º Prevention
19,500 pts

F/U: 30 days, 4, 8, 12 months, and 6 months thereafter

F/U 1 yr minimum

1º EP: Composite of CV death, MI, Stroke, urgent revascularization and Recurrent Ischemia w/ Rehosp

1º EP: Composite of CV death, MI, Stroke, and urgent revascularization
to be continued !!!!!!!!!!